



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p><b>(54) Title:</b> COMPOSITIONS AND METHODS FOR MODULATING SEXUAL ACTIVITY</p> <p><b>(57) Abstract</b></p> <p>The present invention discloses that substituted acetic acid derivatives containing a piperazine moiety are useful as pro-libido agents for males and females, and may be used for the treatment of sexual dysfunction including erectile dysfunction and impotence and to enhance sexual performance.</p>			

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## COMPOSITIONS AND METHODS FOR MODULATING SEXUAL ACTIVITY

### TECHNICAL FIELD

The present invention is generally directed to piperazine derivatives of substituted acetic acids and pharmaceutical compositions thereof, to the preparation of such compounds and compositions, and to the use of such compounds and compositions to enhance sexual performance, as pro-libido agents and/or for the treatment and/or prevention of sexual dysfunction in male and/or female animals.

### BACKGROUND OF THE INVENTION

At the present time there is a wide variety of pharmacological agents used and/or reportedly useful as pro-libido agents and/or for the treatment of sexual dysfunction. Some examples include: serotonin receptor agonists and antagonists (*see, e.g.*, EP 385,658; WO 94/15,920; GB 2,248,449; and GB 2,276,165), dopamine receptor agonists (*see, e.g.*, WO 93/23,035; WO 94/21,608; Pomerantz S. M., 15 *Pharmacol. Biochem. Behav.* 39:123-128, 1991; and Ferrari F. et al. *Psychopharmacology* 113:172-176, 1993); adrenergic receptor agonists (*see, e.g.*, WO 95/13,072; EP 611,248; US 5,229,387; and WO 92/11,851); inhibitors of phosphodiesterase (*see, e.g.*, DE 4,338,948; and WO 94/28,902); histamine receptor agonists (*see, e.g.*, US 4,013,659; US 4,126,670; US 4,767,778; WO 91/17,146; US 20 5,047,418; and EP 0,458,661); neuropeptide Y antagonists (*see, e.g.*, WO 95/00,161); angiotensin II receptor antagonists (*see, e.g.*, EP 577,025); cholinesterase inhibitors (*see, e.g.*, US 5,177,070; and US 4,633,318); combinations of agents with the different types of biological activity (*see, e.g.*, US 5,145,852; and WO 95/05,188); derivatives of vasoactive intestinal peptide (*see, e.g.*, US 5,147,855; EP 540,969; and EP 463,450); 25 prostaglandins (*see, e.g.*, WO 93/00,894; and EP 459,3770); antidepressants and antipsychotics (*see, e.g.*, US 4,931,445; GB 2,448,449; and Naganuma et al. *Clin. Exp. Pharm. Physiol.* 20:177-183, 1993); nitric oxide donors (*see, e.g.*, WO 92/21,346; DE 4,305,881; DE 4,212,582; and WO 94/16,729); calcitonin gene related peptide (*see,*

e.g., Steif, C. G. et al., *Urology*, 41:397-400, 1993); and androgens (see, e.g., JP 06,211,675; HU 62,473; and WO 94/16,709).

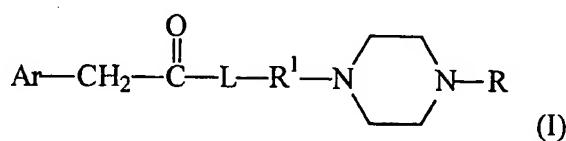
Many or all of these pharmacological agents are associated with adverse effects, some examples of which are quoted below. Dopamine receptor agonists may 5 aggravate schizophrenia or induce it *de novo* in some patients. Serotonin receptor agonists are capable of producing an effect that has been termed "serotonin syndrome" (Glennon, R.A. *J. Med. Chem.* 30:1-9,1987). This latter effect has been thoroughly investigated in animals (Peroutka, S. J. *Science* 212:827-829, 1981; Goddwin G. M. et al., *Br. J. Pharmacol.* 84:743-753, 1985; and Tricklebank, M. D., *Eur. J. Pharmac.* 10 117:15-24, 1985) and manifests itself in, for example, head twitches, "wet dog shakes", forepaw treading, flat body posture, hind limb abduction, Straub tail and yawning. Histamine receptor agonists may induce central nervous system dysfunction and adverse effects in the endocrine system. Smooth muscle relaxants (such as papaverine) may induce pain, echymosis and occasional episodes of priapism.  $\alpha$ -Adrenoreceptor 15 blockers administered systemically have been reported to induce priapism characterized by a persistent erection that cannot be relieved by sexual intercourse or masturbation (Kaisary, A.V. et al., *Br. J. Urol.* 68:227, 1986).

Accordingly there is a need in the art to identify new pharmacological agents, compositions and/or treatments which are useful as pro-libido agents and/or are 20 useful in the treatment and/or prevention of sexual dysfunction in males or females, and/or can enhance a patient's sexual performance. The present invention fulfills these needs and further provides related advantages.

## SUMMARY OF THE INVENTION

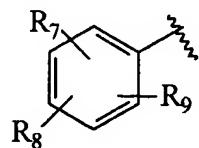
Briefly, one aspect of the invention provides compounds of formula (I)

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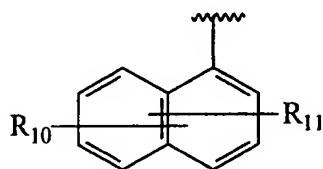
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):

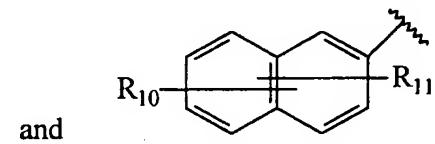


(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from  
10 hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

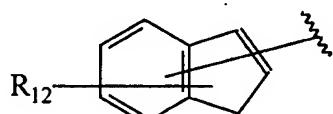


(III)



(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy,  
15 hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

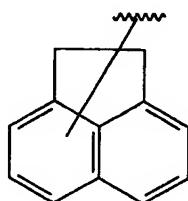


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(V)

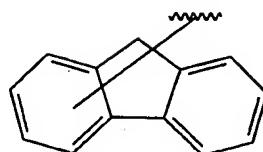
where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and

$N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1-C_6$ alkyl;



(VI)

and



(VII),

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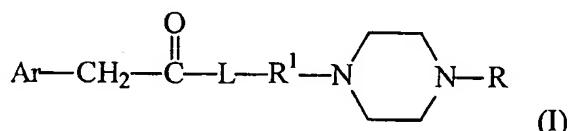
$L$  is selected from the group of a direct bond,  $O$ ,  $NH$ , and  $N(C_1-C_6$  alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1-C_6$  alkylene group, (such as  $-CH_2-$  and  $-CH_2CH_2-$ ), and 1,2-disubstituted  $C_5-C_6$  cycloalkyl; and

$R$  is H or an aralkyl group.

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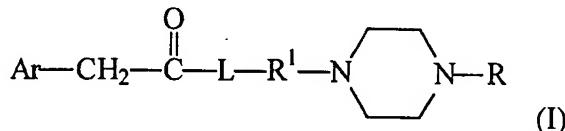
Another aspect of the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent in combination with a compound of formula (I):



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definition set forth above.

15 Another aspect of the invention provides a method for treating and/or preventing sexual dysfunction in a male or female patient, where the method includes the step of administering to the patient in need thereof an amount of a compound of formula (I) or composition therefrom,

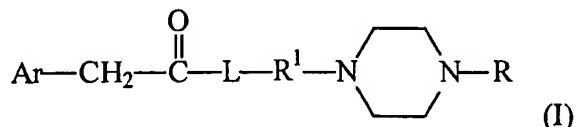
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including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definition set forth above, and where the

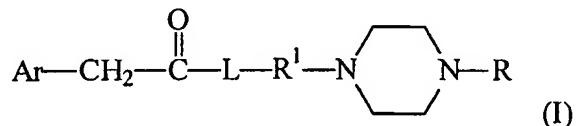
amount is effective to treat and/or prevent the sexual dysfunction. The sexual dysfunction may be, for example, male erectile dysfunction or impotence.

Another aspect of the invention provides a use of a compound for manufacture of a medicament for treating and/or preventing sexual dysfunction in a 5 male or female patient, wherein the compound is of formula (I):



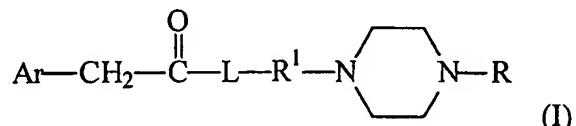
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above. The sexual dysfunction may be, for example, male erectile dysfunction or impotence.

10 Another aspect of the invention provides a method for increasing the libido of a male or female patient, where the method includes the step of administering to a male or female in need thereof an effective amount of a compound, or composition therefrom, of formula (I):



15 including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above, and where the amount is effective to increase the libido of the patient.

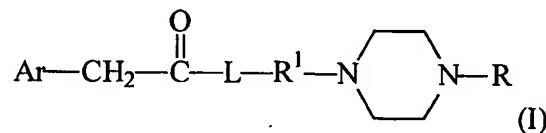
Another aspect of the invention provides a use of a compound, or 20 composition therefrom, for manufacture of a medicament for increasing the libido of a male or female patient, wherein the compound is of formula (I):



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above.

Another aspect of the invention provides a method for enhancing the sexual performance of a male or female patient, comprising administering to the patient in need thereof a therapeutically effective amount of a compound, or composition therefrom, of the formula (I):

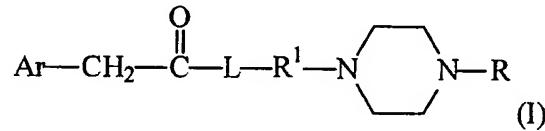
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including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above, and wherein  
10 the amount increases the sexual performance of the patient.

Another aspect of the invention provides a use of a compound, or composition therefrom, for manufacture of a medicament for enhancing the sexual performance of a male or female patient, wherein the compound is of formula (I)

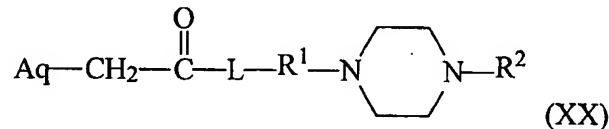
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including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above.

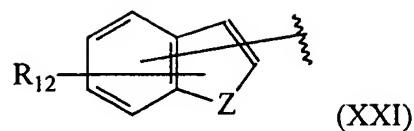
Another aspect of the invention provides compounds of formula (XX)

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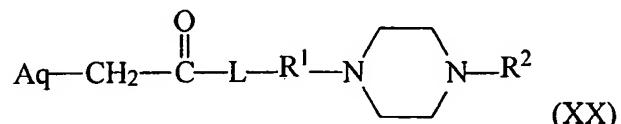
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system of the formula (XXI)



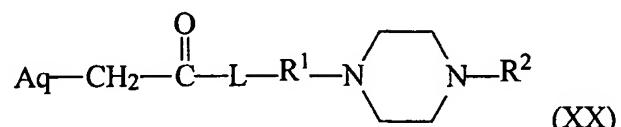
where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_6$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and 5  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and  $Z$  is selected from O, N and S, where  $Z$  may be directly bonded to “- $CH_2C(O)-L-$ ” as shown in formula (XX) when  $Z$  is N, or  $Z$  may be directly bonded to  $R_{17}$ , when  $Z$  is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$  alkyl, 10  $C_3$ - $C_8$  cycloalkyl, aryl and benzyl; L is selected from the group of a direct bond, O, NH, and  $N(C_1-C_6$  alkyl);  $R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$  alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$  cycloalkyl; and  $R^2$  is selected from the group of H, 15 a  $C_1$ - $C_6$  alkyl and a  $C_7$ - $C_{13}$  aralkyl group.

Another aspect of the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent in combination with a 15 compound of formula (XX):



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definition set forth above.

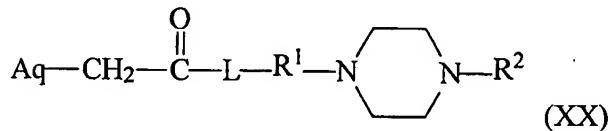
Another aspect of the invention provides a method for treating or 20 preventing sexual dysfunction in a patient, comprising administering to the patient in need thereof an amount of a compound, or composition therefrom, of the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definition set forth above, and

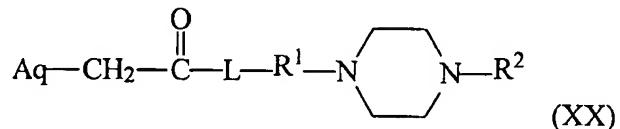
where the amount is effective to treat or prevent the sexual dysfunction of the patient. In the method, the sexual dysfunction may be, for example, male erectile dysfunction, or impotence.

- Another aspect of the invention provides a use of a compound for  
 5 manufacture of a medicament for treating and/or preventing sexual dysfunction in a male or female patient, wherein the compound is of formula (XX):



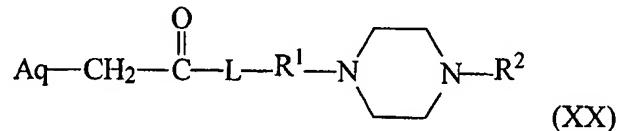
- including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definition set forth above. The  
 10 sexual dysfunction may be, for example, male erectile dysfunction or impotence.

In another aspect, the invention provides a method for increasing the libido of a male or female patient, comprising administering to the patient in need thereof an amount of a compound, or composition therefrom, of the formula (XX)



- 15 including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above, and where the amount is effective to increase the libido of the patient.

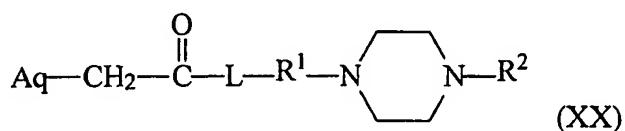
- Another aspect of the invention provides a use of a compound, or  
 composition therefrom, for manufacture of a medicament for increasing the libido of a  
 20 male or female patient, wherein the compound is of formula (XX):



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above.

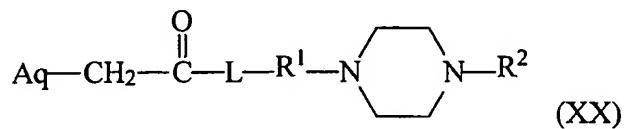
In another aspect, the invention provides a method for enhancing the sexual performance of a male or female patient, comprising administering to the patient in need thereof an amount of a compound, or composition therefrom, of the formula (XX)

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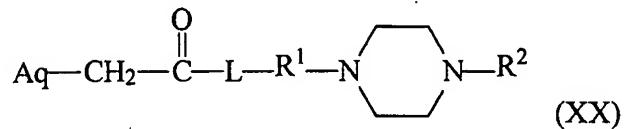
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above, and wherein the amount is effective to enhance the sexual performance of the patient.

Another aspect of the invention provides a use of a compound, or  
10 composition therefrom, for manufacture of a medicament for enhancing the sexual performance of a male or female patient, wherein the compound is of formula (XX)



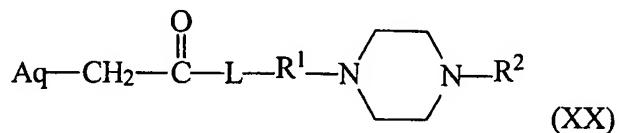
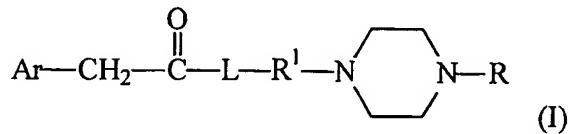
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above.

15 In another aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of the formula (XX)



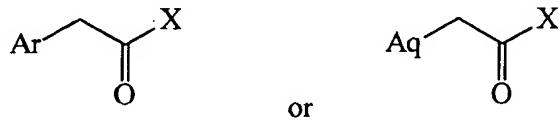
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, which has the definition set forth above; and wherein the composition is in the form of a tablet for oral administration, and the tablet has a disintegration time of less than one hour.

Another aspect of the invention is a method for the preparation of a compound of formula (I) or formula (XX), as defined above,



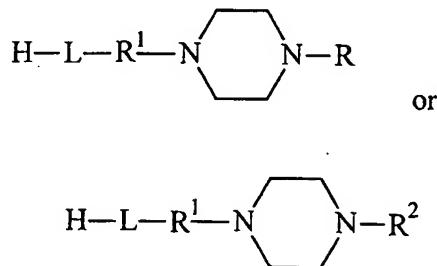
5 including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, having the definitions set forth above. According to the inventive method, a substituted acetic acid compound or activated version thereof having the formula

10



wherein X is OH or an activated (leaving) group such as chloride, is reacted with a compound having the formula

15



The reaction provides a bond between C=O and L as shown in formulae (I) and (XX) above.

These and other aspects of the invention will be more fully understood upon reference to the following detailed description and examples.

## DETAILED DESCRIPTION OF THE INVENTION

An understanding of the present invention may be aided by reference to the following definitions and explanation of conventions used herein.

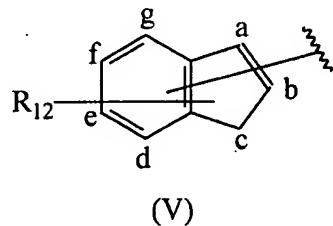
### Definitions and Conventions

5 In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular  
10 substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position.

In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be  
15 present at different atoms of the ring, or on the same atom of the ring, so long as that atom could otherwise be substituted with a hydrogen atom.

Likewise, where the invention specifies compounds containing the Ar-CH<sub>2</sub>C(O)-L- group where Ar equals the group (V)

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the invention is intended to encompass compounds wherein -CH<sub>2</sub>C(O)-L- is joined through CH<sub>2</sub> to the Ar group (V) at any atom which forms the group (V) so long as that atom of group (V) could otherwise be substituted with a hydrogen atom. Thus, there are seven positions (identified with the letters "a" through "g") in structure (V) where the -CH<sub>2</sub>C(O)-L- group could be attached, and it is attached at one of those seven

positions. The R<sub>12</sub> group would occupy one and only one of the remaining six positions, and hydrogen atoms would be present in each of the five remaining positions.

The compounds of the present invention may contain two or more asymmetric carbon atoms and thus exist as enantiomers and diastereomers. Unless 5 otherwise noted, the present invention includes all enantiomeric and diastereomeric forms of the compounds of the invention. Pure stereoisomers, mixtures of enantiomers and/or diastereomers, and mixtures of different compounds of the invention are included within the present invention. Thus, compounds of the present invention may occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers 10 with all isomeric forms being included in the present invention. A racemate or racemic mixture does not imply only a 50:50 mixture of stereoisomers. The compounds of formula (I) or formula (XX) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The phrase "independently at each occurrence" is intended to mean (i) 15 when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (*e.g.*, R<sub>1</sub> within the set R<sub>1</sub> and R<sub>2</sub>) is selected without regard the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if 20 such combinations result in stable compounds.

In accordance with the present invention and as used herein, the following terms are defined to have following meanings, unless explicitly stated otherwise:

"Acid addition salts" refers to those salts which retain the biological 25 effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid,

cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

“Acyl” refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl -(C=O)- group containing the specified number of carbon atoms. Examples include acetyl [CH<sub>3</sub>C(=O)-, a C<sub>2</sub>acyl] and propionyl [CH<sub>3</sub>CH<sub>2</sub>(C=O)-, a C<sub>3</sub>acyl].

“Alkanoyloxy” refers to an ester substituent wherein the non-carbonyl oxygen is the point of attachment to the molecule. Examples include propanoyloxy [(CH<sub>3</sub>CH<sub>2</sub>(C=O)-O-, a C<sub>3</sub>alkanoyloxy] and ethanoyloxy [CH<sub>3</sub>(C=O)-O-, a C<sub>2</sub>alkanoyloxy].

“Alkoxy” refers to an O-atom substituted by an alkyl group, for example, methoxy [-OCH<sub>3</sub>, a C<sub>1</sub>alkoxy].

“Alkoxyalkyl” refers to an alkylene group substituted with an alkoxy group. For example, methoxyethyl [CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>-] and ethoxymethyl (CH<sub>3</sub>CH<sub>2</sub>OCH<sub>2</sub>-) are both C<sub>2</sub>alkoxyalkyl groups.

“Alcoxycarbonyl” refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl [CH<sub>3</sub>CH<sub>2</sub>O(C=O)-, a C<sub>3</sub>alkoxycarbonyl] and methoxycarbonyl [CH<sub>3</sub>O(C=O)-, a C<sub>2</sub>alkoxycarbonyl].

“Alkyl” refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C<sub>3</sub>alkyl), *iso*-propyl (also a C<sub>3</sub>alkyl), and *t*-butyl (a C<sub>4</sub>alkyl).

“Alkylene” refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, a C<sub>3</sub>alkylene].

“Alkylcarboxy” refers to a branched or unbranched hydrocarbon fragment terminated by a carboxylic acid group [-COOH]. Examples include

carboxymethyl [HOOC-CH<sub>2</sub>-, a C<sub>2</sub>alkylcarboxy] and carboxyethyl [HOOC-CH<sub>2</sub>CH<sub>2</sub>-, a C<sub>3</sub>alkylcarboxy].

“Aryl” refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, where phenyl and naphthyl groups are preferred carbocyclic aryl groups.

“Aralkyl” refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example of an aralkyl group is the benzyl group [C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>-, a C<sub>1</sub>aralkyl group].

“Cycloalkyl” refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group (C<sub>5</sub>H<sub>7</sub>-), which is a five carbon (C<sub>5</sub>) unsaturated cycloalkyl group.

“Carbocyclic” refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

“Carbocyclic aryl” refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

“Heteroatom” refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present invention.

“Heteroaryl” refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in “Handbook of Chemistry and Physics,” 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable

heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

“Hydroxyalkyl” refers to a branched or unbranched hydrocarbon fragment substituted with an hydroxy (-OH) group. Examples include hydroxymethyl 5 (-CH<sub>2</sub>OH, a C<sub>1</sub>hydroxyalkyl) and 1-hydroxyethyl (-CHOHCH<sub>3</sub>, a C<sub>2</sub>hydroxyalkyl).

“Thioalkyl” refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH<sub>3</sub>S-, a C<sub>1</sub>thioalkyl).

As used herein, the term patient refers to a warm-blooded animal such as a mammal which can and will benefit from the above treatment (curative or prophylactic). It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of male and female patients within the scope of the meaning of the term.

“Pharmaceutically acceptable carriers” for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. Id. at 1449. In addition, 20 antioxidants and suspending agents may be used. Id.

“Pharmaceutically acceptable salt” refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or 25 salt forms, with both forms being considered as being within the scope of the present invention.

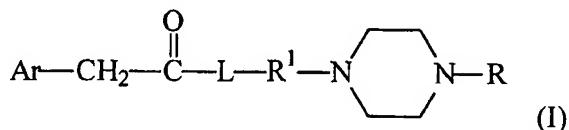
The “therapeutically effective amount” of a compound of the present invention will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal 30 under consideration. These factors and their relationship to determining this amount are

well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

5 Compositions described herein as "containing a compound of formula (I)" or "containing a compound of formula (XX)", etc. encompass compositions that contain more than one compound of formula (I), or formula (XX), etc.

Compounds of the Present Invention

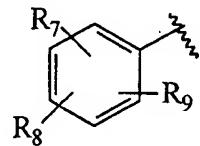
10 As noted above, in one aspect, the present invention is directed toward compounds having formula (I)



15 including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof. In the compounds, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII) wherein compounds having each of the ring systems represented by formulae (II), (III), (IV), (V), (VI), and (VII) independently represent preferred sets of compounds of the invention:

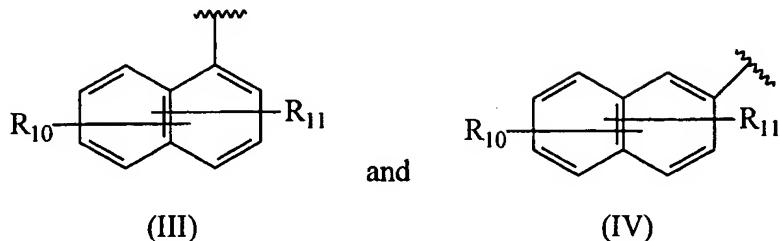
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(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl,

$C_1$ - $C_6$ thioalkyl, aryl and  $N(R_{15}, R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl;

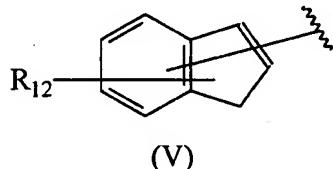


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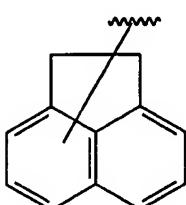
(III)

(IV)

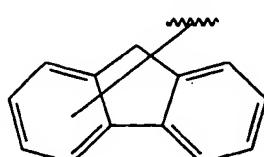
where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;



where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15}, R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



and



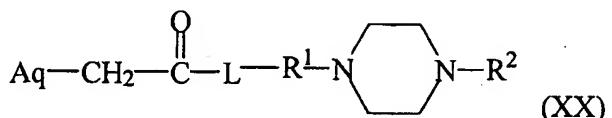
(VI)

(VII):

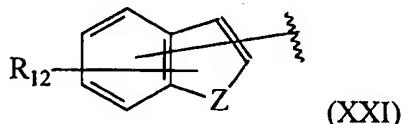
L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl); R<sup>1</sup> is selected from a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group (such as -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-), and 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and

R is H or a C<sub>7</sub>-C<sub>13</sub>aralkyl group.

As also noted above, in another aspect the present invention is directed toward compounds having formula (XX)



- 5 including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof. In the compounds of formula (XX), Aq is a heterocyclic ring system having, for example, the formula (XXI)



- 10 where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl; and Z is selected from O, N and S, where Z may be directly bonded to "-CH<sub>2</sub>C(O)-L-" as shown in formula (XX) when Z is N, or Z may be directly bonded to R<sub>17</sub> when Z is N, and R<sub>17</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, aryl and benzyl; L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl); R<sup>1</sup> is selected from a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group (such as -CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>-), and 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and R<sup>2</sup> is selected from  
15 the group of H, a C<sub>1</sub>-C<sub>6</sub> alkyl and a C<sub>7</sub>-C<sub>13</sub>aralkyl.  
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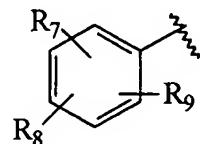
These compounds of formulae (I) and (XX) are included herein with the term "compounds of the invention" or "the inventive compounds" or "substituted acetic acid derivatives of the invention", or the like. In a preferred embodiment, Ar is an aryl group.

- 25 In general, compounds of the present invention may be in the form of a solvate or salt, preferably a pharmaceutically acceptable solvate or salt, e.g., an acid addition salt. Such salts include, without limitation, hydrochloride, sulfate, phosphate,

citrate, fumarate, methanesulphonate, acetate, tartrate, maleate, lactate, mandelate, salicylate, succinate and other salts known in the art.

The Ar or Aq group is preferably but not necessarily a hydrophobic moiety. Typically, a hydrophobic moiety is comprised of non-polar chemical groups such as hydrocarbons or hydrocarbons substituted with halogens or ethers or heterocyclic groups containing nitrogen, oxygen, or sulfur ring atoms. Suitable hydrocarbons are C<sub>3</sub>-C<sub>13</sub> carbocyclic rings. Particularly preferred cyclic hydrocarbons include selected aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, indenyl, acenaphthyl, and fluorenyl and are represented by formulae (II), (III), (IV), (V), (VI), or (VII) respectively.

A suitable Ar group within the compounds of the present invention is a phenyl ring represented by formula (II):



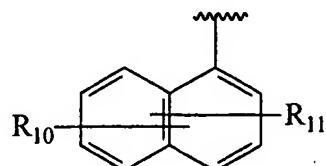
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(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl.

Other suitable Ar groups in compounds of the present invention are 1-naphthyl groups as represented by formula (III):

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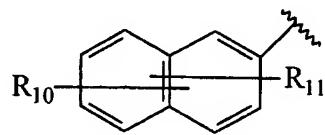


(III)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, 5 C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl.

Other suitable Ar groups in compounds of the present invention are 2-naphthyl group as represented by formula (IV):

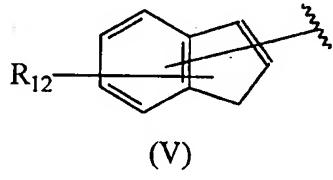
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(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, 15 hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl, as defined above.

Other suitable Ar groups in compounds of the present invention are 20 aromatic groups represented by formula (V):



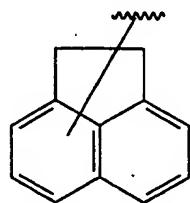
(V)

25 where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and

$N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl.

Another suitable Ar group in compounds of the present invention is the acenaphthyl group as represented by formula (VI):

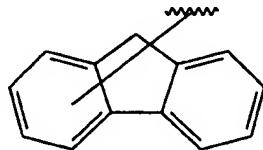
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(VI)

10 Still another suitable Ar group in compounds of the present invention is the fluorenyl group as represented by formula (VII):

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(VII)

In further preferred embodiments, the acenaphthyl group is a 1-acenaphthyl group, and the fluorenyl group is a 9-fluorenyl group.

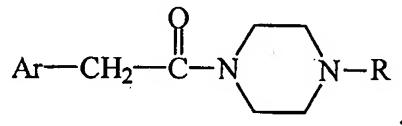
20 In other preferred embodiments of the invention, L is O, or NH, or  $N(C_1$ - $C_6$ alkyl).  $N(C_1$ - $C_6$ alkyl) refers to an alkyl-substituted N (nitrogen) atom, where the alkyl group has at least one and no more than six carbon atoms. These carbon atoms may be arranged in any linear, branched or cyclic fashion. Exemplary alkyl groups encompassed by  $C_1$ - $C_6$  alkyl include, without limitation, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *t*-butyl, *sec*-butyl, *t*-butyl, cyclopropyl and cyclobutyl, cyclopentyl, 25 methyl-substituted cyclopentyl (all isomers), and cyclohexyl, to name a few. A preferred alkyl group which may be bonded to the nitrogen atom is methyl.

In other preferred embodiments of the invention, for each of L being O (oxygen), NH or  $N(C_1$ - $C_6$ alkyl),  $R^1$  is a  $C_1$ - $C_6$ alkylene group, or a 1,2-disubstituted

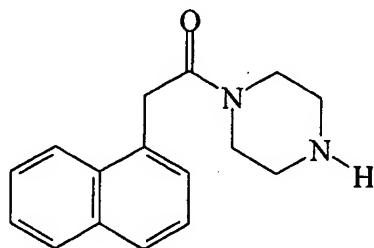
$C_5$ -cycloalkyl (*i.e.*, 1,2-disubstituted cyclopentyl ring) or a 1,2-disubstituted  $C_6$ -cycloalkyl (*i.e.*, 1,2-disubstituted cyclohexyl ring). In another preferred embodiment, compounds of the invention have L and R<sup>1</sup> both being direct bonds.

The  $C_1$ - $C_6$ alkylene group has at least one, and as many as six carbon atoms. These carbon atoms may be arranged in a linear or branched fashion, so long as the carbon atoms have two open valencies for bonding to L and one nitrogen of the piperazine moiety. Exemplary  $C_1$ - $C_6$ alkylene groups include, without limitation, -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)-, which illustrate both linear and branched arrangements, and the lower end (C<sub>1</sub>) and the upper end (C<sub>6</sub>) of the alkylene chain.

In another preferred embodiment of compounds of the invention, when R<sup>1</sup> is a direct bond, then L is also a direct bond. Thus, preferred compounds of the invention have the formula

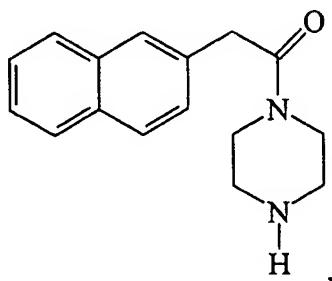


including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof. According to this embodiment of the invention, a preferred compound has Ar equal to 1-naphthyl as described in Example 4, and has the following structure



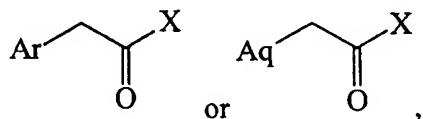
including salts, solvates, isolated tautomers, and mixtures thereof.

Also according to this embodiment of the invention, another preferred compounds has Ar equal to 2-naphthyl, and is described in Example 5, and has the following structure

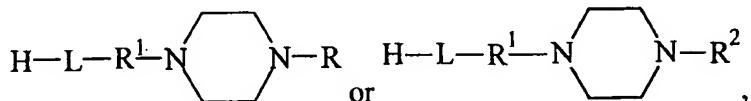


- 5 including salts, solvates, and mixtures thereof.

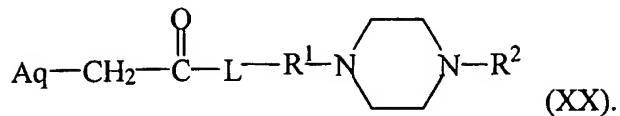
Certain compounds of the invention may be prepared by a method wherein a substituted acetic acid compound or activated version thereof, having the formula



- 10 wherein X is OH or an activated (leaving) group such as chloride, is reacted accordingly with a compound of the formula



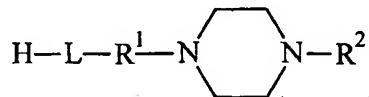
- For compounds where R or R<sup>2</sup> is H, it is preferred that selective protection of these N-H functions (e.g., in the form of a t-Boc (N-tert-butoxy-carbonyl) group) is carried out prior to reaction with a substituted acetic acid compound or activated version thereof. Examples 4 and 5 illustrate the use of the t-Boc protective group in two different conjugation reactions. Conditions for removal of the t-Boc function are described also. Other suitable protecting groups and conditions for deprotection are set forth in, for 20 example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Son, New York, N.Y. (1991). The reaction provides a bond between C=O and L as shown in the formula below, when the acid chloride contains the Aq group.



Compounds of formula Ar-CH<sub>2</sub>-C(=O)-X, or Aq-CH<sub>2</sub>-C(=O)-X, wherein X is other than -OH, may be prepared from the corresponding acid (where X is -OH). These acid starting materials, such as 1-naphthalene acetic acid, 2-naphthalene acetic acid, phenylacetic acid, bromophenylacetic acid (including the 2-, 3- and 4- positional isomers), methylphenylacetic acid (also known as tolylactic acid) and many other compounds of the formula Ar-CH<sub>2</sub>-COOH are commercially available. See, e.g., Aldrich Chemical Co., Milwaukee, WI.

A substituted acetic acid may be reacted with, e.g., thionyl chloride, to 10 prepare an activated substituted acetic acid compound. Other synthetic protocols for preparing an activated acid may be found in, e.g., Szmuszkovicz, J.; Von Voigtlander, P.F. (1982) *J. Med. Chem.* 25: 1125-1126; U.S. Patent 5,506,257 to MacLeod B.A. et al., U.S. Patent 5,637,583 to MacLeod B.A. et al. and Clark, C.R. et al. (1988) *J. Med. Chem.* 31: 831-836.

15 The activated substituted acetic acid compound is then reacted with an amine or alcohol compound (depending on the identity of L) of the formula



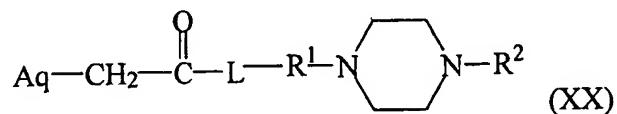
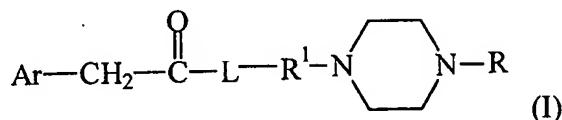
For compounds where R<sup>1</sup> is a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub>cycloalkyl the following references provide some methods for their preparation. The preparation of 20 1,2-diaminocyclohexyl intermediates is described in, e.g., Szmuszkovicz, J.; Von Voigtlander, P.F. (1982) *J. Med. Chem.* 25: 1125-1126; and U.S. Patent 5,506,257 to MacLeod B. A. et al. The preparation of 1-hydroxy-2-aminocyclohexyl intermediate is described in U.S. Patent 5,637,583, also to MacLeod B.A. et al. The preparation of reactive carboxylic acid derivatives is described in the above references as well as in 25 Clark, C. R. et al. (1988) *J. Med. Chem.* 31: 831-836.

Alternatively the carboxylic acids may be coupled to the amine in the presence of a coupling reagent such as dicyclohexyl carbodiimide (DCC) or the like. The reaction is generally carried out in a suitable solvent such as tetrahydrofuran or dioxane at ambient temperature, but depending upon the reactivity of the specific starting materials employed, the reaction time, solvent employed and reaction temperature may be varied without undue experimentation by one of ordinary skill in the art, to achieve the desired coupling reaction. A reaction temperature of between about -25°C and the boiling point of the solvent are typically employed. The reaction between the activated carboxylic acid (*e.g.*, acid chloride) and the amine is generally carried out at ambient temperature in a suitable solvent such as chloroform or dichloromethane in the presence of an acid acceptor (*i.e.*, base) such as a tertiary amine or an alkaline metal carbonate or bicarbonate. The mixture of amine and acid halide is allowed to react until the reaction is essentially complete.

**15 Compositions of the Present Invention**

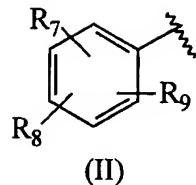
The present invention provides compositions, preferably pharmaceutical compositions, which contain at least one compound of the present invention as set forth above, and at least one pharmaceutically acceptable carrier or diluent, where the compounds of the present invention have formulae (I) or (XX)

20

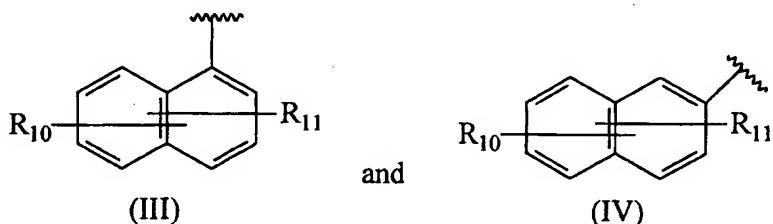


including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein,

25 Ar is selected from a C<sub>3</sub>-C<sub>13</sub>carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):



where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;



10

(III)

and

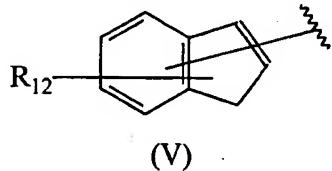
(IV)

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15 independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;

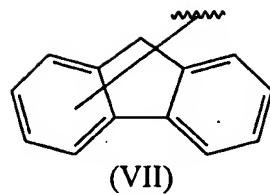
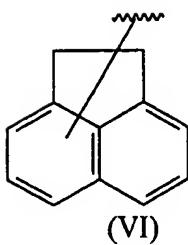
**Figure 1.** Schematic diagram of the structure of the polyimide film.

$R_{12}$



(V)

where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl; and

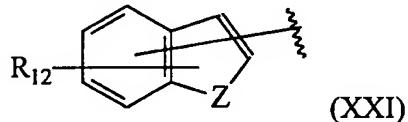


including isolated enantiomeric, diastereomeric, tautomeric, and geometric isomers thereof, and mixtures thereof;

5 L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);  
and

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group,  
and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl.

In the compositions having compounds of formula (XX), Aq is a  
10 heterocyclic ring system having the formula (XXI)



where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  
15 C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl; and Z is selected from O, N and S, where Z may be directly bonded to "-CH<sub>2</sub>C(O)-L-" as shown in formula (XX) when Z is N, or Z may be directly bonded to R<sub>17</sub> when Z is N, and R<sub>17</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
20 C<sub>3</sub>-C<sub>8</sub> cycloalkyl, aryl and benzyl; L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl); R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and R<sup>2</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl,

A composition may include, for example, water. In a preferred embodiment, the composition is in the form of a tablet, and particularly a fast-release tablet for oral administration. A fast-release tablet (having a rapid disintegration time)

is desired in order to provide the patient with a rapid onset of enhanced sexual performance and/or increased libido and/or relief of sexual dysfunction.

A "fast-release" tablet will have a disintegration time of less than about one hour, preferably less than about 20 minutes, and more preferably less than about 5 two or even one minutes. A suitable fast-release tablet contains 40 mg of a compound of the present invention, 8 mg of silicon dioxide (NF), 4 mg of stearic acid (NF), 212 mg of lactose (NF), 120 mg of microcrystalline cellulose (NF) and 16 mg of croscarmellose sodium (NF). A tablet containing these ingredients may be prepared by finely dividing and then mixing each ingredient together, then compressing the mixture 10 into a tablet form. The tablet has a weight of about 400 mg. Other methods of mixing and tablet formulation will be readily apparent to one of ordinary skill in the art. A tablet prepared by this method will typically have a hardness of 10.7 Kp, an average thickness of about 0.2 inches and an average disintegration time of about 45 minutes.

Disintegrant compounds, such as croscarmellose sodium (NF) (available 15 as Ac-Di-Sol from FMC Corporation), may be used to enhance the dissolution time of a formulation of the present invention. Other disintegrants such as potato starch, Explotab<sup>TM</sup> sodium starch glycolate, Polyplasdone<sup>TM</sup> XL crospovidone NF, Starch 1500<sup>TM</sup> pregelatinized starch NF may be employed in the formulations of the present invention. Each of U.S. Patent Nos. 5,731,339, 5,298,261 and 5,079,018 also describe 20 formulations which demonstrate fast disintegration times, which may be employed to prepare a fast release formulation of the present invention.

Suitable disintegrants and methods for measuring disintegration time of tablets are described in Gissinger et al. "A Comparative Evaluation of the Properties of some Table Disintegrants" *Drug Development and Industrial Pharmacy* 6(5):511-536 25 (1980); and *European Pharmacopeia* 1980.

The pharmaceutical compositions of the present invention may be in any form which allows for the composition to be administered to a patient. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, oral, topical, parenteral (*e.g.*, sublingually or 30 buccally), sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein

includes subcutaneous injections, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, intraurethral injection or infusion techniques. Pharmaceutical composition of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition

5 to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of one or more compounds of the invention in aerosol form may hold a plurality of dosage units.

For oral administration, an excipient and/or binder may be present.

10 Examples are sucrose, kaolin, glycerin, starch dextrins, sodium alginate, carboxymethylcellulose and ethyl cellulose. Coloring and/or flavoring agents may be present. A coating shell may be employed.

The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for

15 delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the inventive compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent

20 may be included.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as

25 synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium

30 chloride or dextrose. The parenteral preparation can be enclosed in ampoules,

disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid compositions intended for either parenteral or oral administration should contain an amount of the inventive compound such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral compositions contain between about 4% and about 50% of the inventive compound. Preferred compositions and preparations according to the present invention 10 are prepared so that a parenteral dosage unit contains between 0.01 to 1% by weight of active compound.

The pharmaceutical composition may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the 15 following: petrolatum, lanolin, polyethylene glycols, beeswax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the 20 inventive compound of from about 0.1 to about 10% w/v (weight per unit volume).

The composition may be intended for rectal administration, in the form, e.g., of a suppository which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and 25 polyethylene glycol.

The compounds of the invention may be administered through use of insert(s), bead(s), timed-release formulation(s), patch(es) or fast-release formulation(s).

It will be evident to those of ordinary skill in the art that the optimal dosage of the substituted acetic acid derivatives of the invention may depend on the 30 weight and physical condition of the patient; on the severity and longevity of the sexual

dysfunction (when the goal is to treat sexual dysfunction); on the particular form of the active ingredient, the manner of administration and the composition employed. It is to be understood that use of a substituted acetic compound of the invention in a chemotherapy can involve such a compound being bound to an agent, for example, a 5 monoclonal or polyclonal antibody, a protein or a liposome, which assist the delivery of said compound.

Therefore, the invention relates further to a pharmaceutical or veterinary composition comprising an effective amount of a substituted acetic acid derivative of formula (I) or formula (XX) provided above, in association with a carrier.

10 In a further embodiment, the present invention is directed to the use of a substituted acetic acid derivative of the formula provided above (which includes physiologically acceptable salts and hydrates), for the manufacture of a medicament for treating, relieving or preventing the effects of sexual dysfunction. Thus, the substituted acetic acid derivatives of formula (I) or formula (XX) provided above may be used for 15 the manufacture of a medicament for treating, relieving or preventing the effects of male sexual dysfunction, preferably erectile inadequacy and inhibited male orgasm, especially erectile inadequacy. The substituted acetic acid derivatives of formula (I) or formula (XX) provided above may also be used for the manufacture of a medicament for treating, relieving or preventing the effects of female sexual dysfunction, preferably 20 sexual arousal disorder and inhibited female orgasm, especially sexual arousal disorder.

In a further embodiment, the present invention provides a method for the treatment of a male or female patient suffering from sexual dysfunction, or a method to prevent sexual dysfunction in a patient (having, for example, a history of sexual dysfunction) comprising the administration thereto of a therapeutically or 25 prophylactically effective amount of a compound of formula (I) or formula (XX), or a composition including same, as provided above. The sexual dysfunction may be, for example, male erectile dysfunction or impotence. A patient that cannot obtain an erection may be treated according to the present invention, while a patient that cannot maintain an erection may receive a prophylactic dose of a compound of the invention in 30 order to prevent premature loss of an erection.

In a still further embodiment, the present invention provides a method for increasing the libido of a male or female patient comprising the administration thereto of a therapeutically effective amount of a compound of formula (I) or formula (XX), or a composition including same, as provided above.

- 5        In a still further embodiment, the present invention provides a method for enhancing the sexual performance of a male or female patient that is not necessarily exhibiting symptoms of sexual dysfunction, comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of a compound of formula (I) or formula (XX), or a composition including same, as provided above.
- 10      Enhanced sexual performance occurs when there is an increase in the type of behavior that is typically associated with the patient's sexual activity or interest in sexual activity. Increased tone in the patient's genitals is one indication of an enhancement of sexual performance. Enhancement of sexual performance may result in, e.g., a pro-erectile response in the patient, or an improvement in erectile function such as any increase in
- 15      the ability of the patient to maintain an erection, to induce or improve ejaculation (e.g., have multiple ejaculations within a shortened period of time), or to induce or improve orgasm.

- The term "therapeutically effective amount" refers to an amount which is effective, upon single or multiple dose administration to the patient, to enhance the
- 20      libido and/or sexual performance of the patient receiving the compound or a composition containing the compound as provided above. Such an amount may serve to treat a sexual dysfunction, e.g., impotence in males, and/or to enhance the sexual desire and/or sexual performance of a patient without a sexual dysfunction. For example, the therapeutically effective amount may be administered to, for example, a
- 25      bull, to promote increased semen ejaculation, where the ejaculated semen is collected and stored for use as it is needed to impregnate female cows in promotion of a breeding program. Increased sexual ejaculation is an example of enhanced sexual performance according to the present invention.

- A therapeutically or prophylactically effective amount of a substituted
- 30      acetic acid derivative of the invention is expected to vary from about 0.01 milligram per

- kilogram of body weight per day (mg/kg/day) to about 200 mg/kg/day. Preferred amounts are expected to vary from about 0.5 to about 80 mg/kg/day. A pharmaceutical composition containing a substituted acetic acid derivative of the invention may contain between 0.01 and 1% by weight of the active substituted acetic acid derivative, and
- 5 between about 5 and 10% by weight glucose in order to increase the osmolarity of the solution. Two illustrative compositions are (1) 5 mg/mL of a substituted acetic acid derivative of the invention and distilled water in 100 mL total volume, and (2) 5 mg/mL of a substituted acetic acid derivative of the invention, 25 mg/mL glucose, and distilled water in 100 mL total volume.
- 10 In effecting treatment of a patient in need of an agent for treating sexual dysfunction and/or enhancing sexual performance and/or a pro-libido agent, a compound of the invention can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral, aerosol, and parenteral routes. For example, compounds of the invention can be administered orally, by
- 15 aerosolization, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. The compounds of the invention may be administered by direct injection into, *e.g.*, the corpus cavernosa (intracavernously). The compounds of the invention may be administered intraurethrally (*e.g.*, via an intraurethral catheter). The compounds of the invention may be administered topically,
- 20 *e.g.*, directly to the penis. The compounds may be administered intrameatally. Oral or aerosol administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition, and other relevant circumstances. *See, e.g.*, Remington's
- 25 Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990).

The compounds can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and

30 standard pharmaceutical practice.

- In another embodiment, the present invention provides compositions comprising a substituted acetic acid derivative of the invention in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, or as pharmaceutical compositions. An assayable amount of a compound of the invention is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of the invention will generally vary from about 0.001% to about 75% of the composition by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of the invention. Examples of suitable inert carriers are water; aqueous buffers, such as those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carriers or excipients.
- More particularly, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a substituted acetic acid derivative as disclosed above, in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.
- The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, solution, suspensions, or the like.
- The compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should preferably contain at least 4% of the compound

of the invention as an active ingredient, but this amount may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. The tablets, pills, capsules and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.01% of a compound of the invention, but this amount may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the inventive compound present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 1% by weight of active compound.

The compounds of the present invention may also be administered by aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase,

bi-phasic, or tri-phasic systems in order to deliver the active ingredient. Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, spacers and the like, which together may form a kit. Preferred aerosols are able to be determined by one skilled in the art.

5       The compounds of this invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, beeswax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Topical formulations may contain a concentration of the  
10      inventive compound of from about 0.1 to about 10% w/v (weight per unit volume).

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as  
15      ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred carrier or diluent.

20       The substituted acetic acid derivatives of the invention may be combined with one or more known pharmacological agents used in the treatment and/or prevention of sexual dysfunction and/or known to enhance the libido and/or sexual performance of a patient receiving the pharmacological agents.

25       The following examples are offered by way of illustration and not by way of limitation.

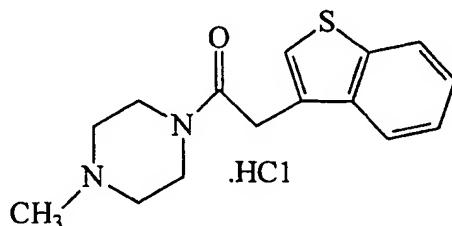
EXAMPLES

In the following Examples, unless otherwise indicated, the reactants, reagents and solvents were of standard commercial grade, and were obtained from 5 Aldrich Chemical Co., Milwaukee, WI, or a similar chemical supply house.

## EXAMPLE 1

## 1-METHYL-4-(3-BENZO[B]THIOPHENACETYL)PIPERAZINE.MONOHYDROCHLORIDE

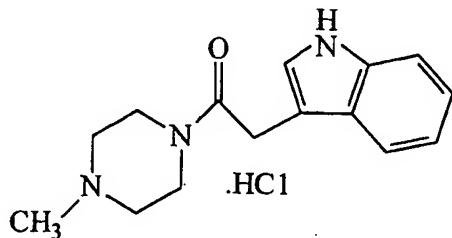
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To a mixture of benzo[b]thiophene-3-acetic acid (1.725 g, 9.0 mmol), 1-methylpiperazine (0.75 g, 7.5 mmol) and triethylamine (1 mL) in anhydrous tetrahydrofuran (70 mL) was added portionwise benzotriazole-1-yl-oxy-tris-pyrrolidino-15 phosphonium hexafluorophosphate "Py-BOP" (4.68 g, 9 mmol). The reaction mixture was then stirred at room temperature for 5 hours. The solvent was evaporated *in vacuo*, the residue was taken up with water (50 mL) and the aqueous solution was basified by addition of 5M NaOH aqueous solution (10 mL). The basic aqueous solution was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue, dissolved in diethyl ether (50 mL), was treated with ethereal HC1 (50 mL). The solution containing the precipitate was then refluxed for 10 min. and the solid was collected. Recrystallization in a mixture of ethanol-ethyl acetate (2:1, v/v, 60 mL) yielded 1.6 g of 20 the title compound. NMR analyses (proton and C-13) and mass spectroscopic analysis 25 of the product are consistent with the structure indicated.

## EXAMPLE 2

## 1-METHYL-4-(3-INDOLACETYL)PIPERAZINE.MONOHYDROCHLORIDE



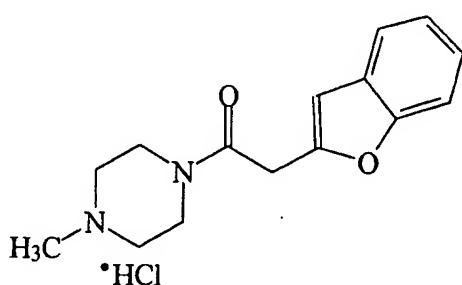
5

To a mixture of indole-3-acetic acid (1.56 g, 9.0 mmol), 1-methylpiperazine (0.75 g, 7.5 mmol) and triethylamine (1 mL) in anhydrous tetrahydrofuran (70 mL) was added portionwise benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate "Py-BOP" (4.68 g, 9 mmol). The reaction mixture 10 was then stirred at room temperature for 5 hours. The precipitate was filtered off and the solvent was evaporated *in vacuo*. The residue was taken up with water (50 mL) and the aqueous solution was basified by addition of 5M NaOH aqueous solution (10 mL). The basic aqueous solution was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in* 15 *vacuo*. The residue, dissolved in ethyl acetate (70 mL), was treated with ethereal HC1 (80 mL). The resulting precipitate was collected. Recrystallization in methanol yielded 0.6 g of the title compound. NMR analyses (proton and C-13) and mass spectroscopic analysis of the product are consistent with the structure indicated.

20

## EXAMPLE 3

## 1-METHYL-4-(2-BENZOFURANACETYL)PIPERAZINE.MONOHYDROCHLORIDE

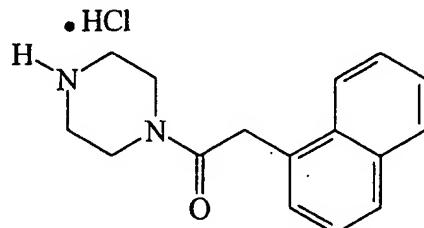


To a mixture of 2-benzofuranacetic acid (0.84 g, 4.8 mmol), 1-methylpiperazine (0.45 g, 4.5 mmol) and triethylamine (0.5 mL) in anhydrous tetrahydrofuran (100 mL) was added portionwise benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate "Py-BOP" (2.5 g, 4.8 mmol).  
 5 The reaction mixture was then stirred at room temperature for 5 hours. The precipitate was filtered off and the solvent was evaporated *in vacuo*. The residue was taken up with water (50 mL) and the aqueous solution was basified by addition of 5M NaOH aqueous solution (8 mL). The basic aqueous solution was extracted with ethyl acetate  
 10 (3 x 30 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue, dissolved in diethyl ether (80 mL), was treated with ethereal HCl (80 mL) and the resulting precipitate was collected. Recrystallization in ethanol yielded 1.2 g of the title compound. NMR analyses (proton and C-13) and mass spectroscopic analysis of the product are consistent with the  
 15 structure indicated.

## EXAMPLE 4

## 1-(NAPHTHYLACETYL)PIPERAZINE.MONOHYDROCHLORIDE

20



25

To a mixture of 1-naphthylacetic acid (1.07 g, 5.7 mmol), *tert*-butyl 1-piperazine carboxylate (1.0 g, 5.4 mmol) and triethylamine (0.7 mL) in anhydrous tetrahydrofuran (50 mL) was added portionwise benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate "Py-BOP" (2.97 g, 5.7 mmol). The reaction mixture was then stirred at room temperature for 5 hours. The precipitate was filtered off and the solvent was evaporated *in vacuo*. The residue was taken up with water (30

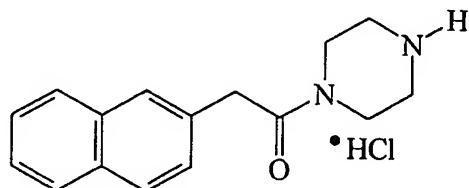
mL) and the aqueous solution was basified by addition of 5M NaOH aqueous solution (10 mL). The basic aqueous solution was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the intermediate N-protected piperazine suitable for the  
5 next step without any further purification.

The N-protected piperazine was treated with 3M HCl ethyl acetate solution (5 mL) to provide a precipitate which was recrystallized from a mixture of toluene-methanol-diethyl ether (1:1, v/v, 30 mL) to yield the title compound. NMR analyses (proton and C-13) and mass spectroscopic analysis of the product are  
10 consistent with the structure indicated.

## EXAMPLE 5

## 2-(NAPHTHYLACETYL)PIPERAZINE.MONOHYDROCHLORIDE

15



2-Naphthylacetic acid (1.86 g, 10 mmol) was refluxed in thionyl chloride (10 mL) for 1 h. After stirring at room temperature for a further 1.5 h, the thionyl chloride was removed *in vacuo* (using 1 x 10 mL and 2 x 5 mL CCl<sub>4</sub>). The residue was dissolved in dichloromethane (15 mL). Then the acid chloride solution was added via cannula to a cooled solution (ice bath) of *tert*-butyl l-piperazine carboxylate (1.86 g, 10 mmol) and triethylamine (1.4 mL, 10 mmol) in dichloromethane (15 mL) under nitrogen. The reaction mixture was diluted with dichloromethane (60 mL) and washed with 1M HCl aqueous solution (50 mL), water (30 mL), 1M sodium bicarbonate aqueous solution (50 mL) and water (30 mL). The organic layer was collected, dried over sodium sulfate and concentrated *in vacuo* to yield the crude intermediate carbamate suitable for the next step without any further purification.  
20  
25

The above carbamate dissolved in ethyl acetate (100 mL) was treated with HCl saturated ethyl acetate solution (50 mL). After a few minutes a precipitate was formed and the reaction mixture was stirred for another 4 hours in order to complete the reaction. The yellow precipitate was collected and recrystallized from 5 ethanol to yield 1.98 g of the title compound. NMR analyses (proton and C-13) and mass spectroscopic analysis of the product are consistent with the structure indicated.

#### EXAMPLE 6

##### EFFECTS OF COMPOUNDS OF THE PRESENT INVENTION ON PROERECTILE ACTIONS

Compounds of the present invention can be tested for their ability to induce erection in male rats according to methods described by Berendsen et al. (*Psychopharmacol.* 1990, 101, 57-61). Male Sprague-Dawley (SD) rats (n=10 per test group) were housed in groups of six, or in pairs, under ambient temperature and light or under reversed 12 hour light cycle and controlled temperature (approx. 22°C) 10 respectively with standard rat chow and water available ad libitum. All test compounds were dissolved in saline or distilled water and injected in a volume of 0.4 to 1 mL/kg. Briefly, animals were injected via an intraperitoneal (i.p.) route with vehicle (saline or distilled water) or test compound and placed individually in clear Plexiglas® cages of 45 15 x 25 x 25 cm for behavioral observation. Erection was scored as described by Berendsen and Broekkamp (*Eur. J. Pharmacol.* 1987, 135, 279-287). Rats housed 20 individually in groups of six to three were treated with vehicle or compounds of the present invention in various doses and, 5 minutes later, observed for the appearance of erection and the latency to first erection over a set period of time (30 to 90 minutes). Alternatively, rats housed individually in groups of six to two were treated with vehicle 25 or compounds of the present invention in various doses 5 minutes prior to a 30 to 60 minutes observation for the occurrence of erection. All treatments were administered in a standard randomized and double-blinded manner. Dose-response data was analysed by ANOVA followed by Dunnett's test for multiple comparisons.

At a dosage of 8 mg/kg, a compound of the present invention as 30 described in Example 4 (1-(Naphthylacetyl)piperazine.monohydrochloride) showed an

average of 4.5 erections per rat (n=3) over a 30 minutes time period of observation with a 100% response rate, whereas in the control rats (n=3, saline) an average of 1.5 erections per rat was observed over the same duration with a 67% response rate.

In another experiment, at a dosage of 8 mg/kg, a compound of the present invention as described in Example 1 (1-Methyl-4-(3-benzo[b]thiophenacetyl)piperazine monohydrochloride) produced an average of 4.7 erections per rat (n=3) over a 60 minutes time period of observation and the average latency to first erection was less than 10 minutes with a 100% response rate, whereas in the control rats (n=3, distilled water) an average of 0.8 erections per rat was observed over the same duration and the average latency to first erection was about 20 minutes with a 100% response rate.

#### EXAMPLE 7

##### EFFECTS OF COMPOUNDS OF THE PRESENT INVENTION ON PROCOPULATORY ACTIONS

The procopulatory actions of compounds of the present invention can be determined by method such as the one described below.

Male Long-Evans rats (300-600 g) were injected via an intraperitoneal (i.p.) route with vehicle (saline or distilled water) or compounds of the present invention 5 minutes prior to being paired with a female rat made sexually receptive by administration of estradiol benzoate (25 µg/kg; 48 hours prior to testing) and progesterone (1 mg/kg; 4 hours prior to testing) (Tanco et al., *Experientia*, 1993, 49, 238-241). Mount latency, intromission latency, ejaculation latency, mounts, intromissions, ejaculations and post ejaculatory interval were recorded over a set observation time period (30-60 minutes) (Watson and Gorzalka, *Neurosci. Lett.*, 1992, 141, 25-29).

## EXAMPLE 8

EFFECTS OF COMPOUNDS OF THE PRESENT INVENTION ON ERECTILE AND EJACULATORY  
RESPONSES

From a procreative perspective pharmacological enhancement of erection 5 loses its value as a treatment for erectile dysfunction if semen production and/or ejaculation are adversely affected. The benefits of pharmacotherapy for the induction of ejaculation are obvious with respect to spinalized patients (Hultling et al., *Hum. Reprod.*, 1995, 10, 847-850) and veterinary medicine (Chung et al., *Obstet. Gynecol.*, 1996, 87, 22-26). The following method can be used to determine the effects of 10 maximally effective erection enhancing doses of compounds of the present invention on seminal emission in male rats.

Male SD rats housed individually in groups of four under reversed light 15 dark cycle were injected i.p. with vehicle (saline or distilled water) or test compound 5 minutes prior to observation of paired rats, in a Plexiglas chamber (40 x 40 x 20 cm), for 1 hour for the occurrence of erection, ejaculation, grooming (penile and non-penile) and yawning. Erections were scored as described previously by Berendsen and Broekkamp (*Eur. J. Pharmacol.* 1987, 135, 279-287) and ejaculation was scored by visual inspection of the rats eating the ejaculate plug. Grooming was scored as being either penile or non-penile according to Sachs et al. (*Physiol. Behav.*, 1988, 43, 20 637-643), with penile grooming being restricted to the genital region and non-penile grooming being any grooming bouts at any region other than the genitalia. Movement was scored as the number of rears during 1 hour and the total number of quadrant crosses during 6 two minute observation periods at 10 minute intervals. Rectal temperature was recorded by thermometer before, and 60 minutes after, vehicle or test 25 compound administration.

## EXAMPLE 9

## EFFECTS OF COMPOUNDS OF THE PRESENT INVENTION ON MOTIVATIONAL ASPECT OF COPULATION

It has been proposed that desire or motivational aspects of sexual function may be different than those of arousal and may be assessed through employment of sexually exhausted male rats (Karen & Barfield, *J. Comp. Physiol. Psychol.*, 1975, 88, 693-703). The following method can be used to assess the effects of compounds of the present invention on motivational aspects of copulation.

Male SD rats (500-600g) were assessed for their ability to copulate to ejaculation, and resume copulation after ejaculation, on 3 separate occasions at 72 hour intervals. Rats were paired with an estrogen (25 µg, t= -48 hours) and progesterone primed (1.5 mg, t= -4 hours) female rats 5 minutes after being placed in circular wire mesh cages 26 cm in diameter. Animals were excluded from use in further studies if they 1) had an ejaculation latency longer than 30 minutes or 2) a post-ejaculatory interval of longer than 15 minutes (Sachs and Barfield, in *Advances in the Study of Behavior*, Academic Press, New York, 1976, Vol.7, p92-154) on any one of the three pre-drug tests. None of the original cohort had a post-ejaculatory interval longer than 15 minutes such that animals included in the drug study had ejaculation latencies shorter than 30 minutes.

Rats selected for drug study were housed individually and allowed to copulate to satiation (4 hours with novel female at 0.5 hour intervals). Twenty-four hours after copulation to satiation the rats were injected with either vehicle (saline or distilled water) or test compound and were again paired with a receptive female rat. Behavioral responses were measured as proportions of animals exhibiting mount, intromission, ejaculation and resumption of copulation after the first ejaculation. The latencies to mount, intromission, ejaculation and resumption of copulation after the first ejaculation, and the number of mounts and intromissions preceding ejaculation were recorded.

## EXAMPLE 10

EFFECTS OF COMPOUNDS OF THE PRESENT INVENTION ON ERECTILE AND DESIRE  
RESPONSES IN MALE PRIMATES

Penile erection is a complexly regulated component of sexual behavior.

- 5 The effects of drugs on penile erection and other aspects of sexual behavior can be more readily studied in rodent species due to the stereotypical nature of rodent sexual behavior patterns in controlled environments (Sachs et al, *Pharmacol. Biochem. Behav.*, 1981, 14, 251-253). In addition to results obtained from rodent studies, methods are available to extend studies to include the use of primates, a species much closer socially  
10 and physiologically to human beings. The methods described below can be used to evaluate the effects of compounds of the present invention on erectile and ejaculatory responses in male primates.

- i) Dose-response study: Male *Macaca fascicularis* (n=6) were housed individually under ambient light and temperature conditions with access to a fruit  
15 supplemented chow diet and water ad libitum. Test animals were taken from the housing facility and transferred, at a site remote from the housing facility, to an observational cage of the same dimensions as the housing cage. Twenty minutes after cage transfer animals were injected with either saline (0.9%) or compounds of the present invention (1.0-10.0 mg/kg) in a volume of 0.5 mL/kg (i.p.). Animals were then  
20 immediately transferred to an empty observational room where, after 10 minutes, penile responses, pursed-lip gesturing and yawning were scored for 1 hour according to methods described by Pomerantz (*Pharmacol. Biochem. Behav.*, 1991, 39, 123-128). Briefly, every 10 seconds the animal was scored for penile tumescence and arousal of the following intensity; grade 0, penile region visible but glans penis not visible; grade  
25 1, glans penis clearly visible; grade 2, penis extended but not fully erect; grade 3, erect penis (less than 90° angle between penis and animal's trunk); grade 4, erection with masturbation and grade 5, erection with masturbation and ejaculation. Pursed-lip gesturing and yawning, affiliative signals believed to be part of courtship behavior (Pomerantz, *Pharmacol. Biochem. Behav.*, 1990, 35, 659-664) were counted as the  
30 number of such behaviors in 1 hour of observation.

ii) Single dose study: In a second set of experiments adult male *Macaca fascicularis* (3.8-8 kg, n=6) were injected with saline, or compounds of the present invention (1.0 mg/kg, i.p.; 0.5 mL/kg body weight) and observed for behavioral responses and locomotion for 1 hour following injection. Monkeys used for testing  
5 were separated from the cluster of housing cages and, dosed and observed in pairs that had visual contact with one another, in the middle of the housing environment.

In the dose-response study, test doses were randomized and a rotation was established such that each monkey received each dose with at least a three day interval between doses. Data for the dose-response study was analysed by repeated  
10 measures ANOVA with Dunnett's test for multiple comparisons. In the single dose study a rotation was established such that of the paired monkeys one received saline and the other received test compound.

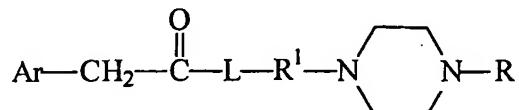
All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication  
15 or patent application was specifically and individually incorporated by reference.

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the  
20 spirit and scope of the present invention as defined by the appended claims.

## CLAIMS

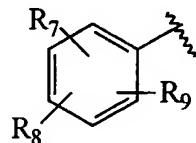
We claim:

1. The use of a compound for the manufacture of a medicament for the treatment or prevention of sexual dysfunction in a patient, the compound having the formula



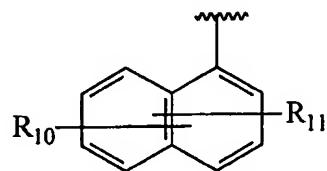
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):

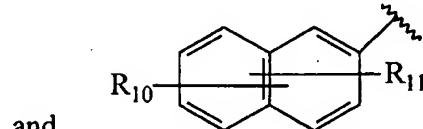


(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen (H), hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;



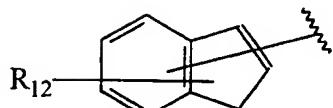
(III)



(IV)

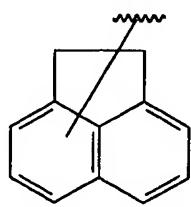
where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and

$N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1-C_6$ alkyl;

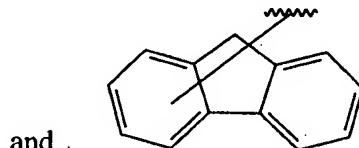


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2-C_7$  alkanoyloxy,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $C_2-C_7$  alkoxy carbonyl,  $C_1-C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1-C_6$  alkyl; and



(VI)



(VII);

$L$  is selected from the group of a direct bond, O, NH, and  $N(C_1-C_6$  alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1-C_6$  alkylene group, and a 1,2-disubstituted  $C_5-C_6$  cycloalkyl; and

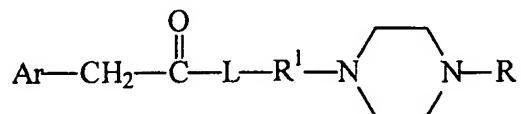
$R$  is H or a  $C_7-C_{13}$  aralkyl;

where the amount is effective to treat or prevent the sexual dysfunction of the patient.

2. The use of claim 1 wherein the sexual dysfunction is male erectile dysfunction.

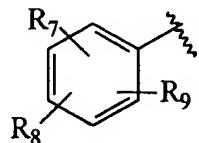
3. The use of claim 1 wherein the sexual dysfunction is impotence.

4. The use of a compound for the manufacture of a medicament for increasing the libido of a male or female patient, the compound having the formula



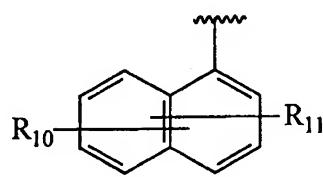
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):

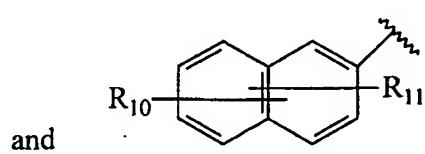


(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

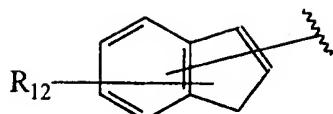


(III)



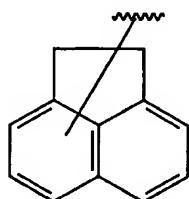
(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

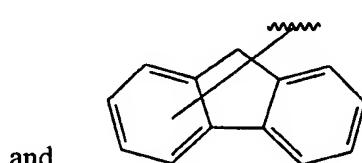


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_6$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15}, R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



(VI)



(VII);

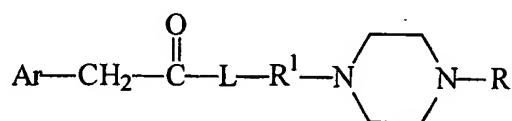
$L$  is selected from the group of a direct bond, O, NH, and  $N(C_1-C_6$  alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$  alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$  cycloalkyl; and

$R$  is H or a  $C_7$ - $C_{13}$  aralkyl;

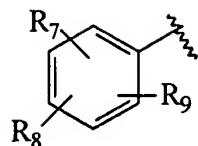
where the amount is effective to increase the libido of the patient.

5. The use of a compound for the manufacture of a medicament for enhancing the sexual performance of a male or female patient, the compound having the formula



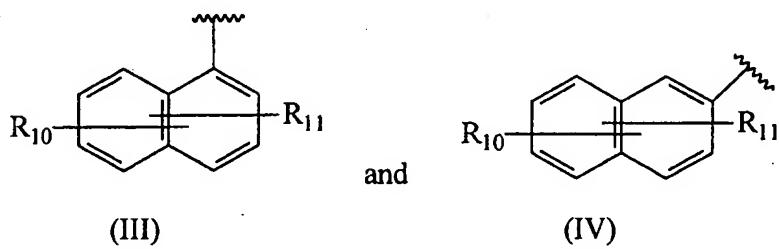
including salts, solvates, isolated enantiomers, isolated diastereomers, and mixtures thereof, wherein, independently at each occurrence:

$\text{Ar}$  is selected from a  $C_3$ - $C_{13}$  carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII);



(II)

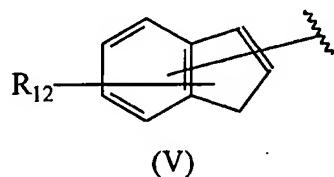
where  $R_7$ ,  $R_8$  and  $R_9$  are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, aryl and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl;



(III)

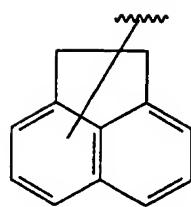
(IV)

where  $R_{10}$  and  $R_{11}$  are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl;

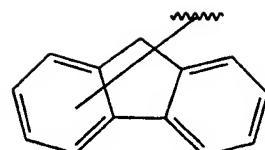


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



(VI)



(VII);

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub>cycloalkyl; and

R is H or a C<sub>7</sub>-C<sub>13</sub>aralkyl;

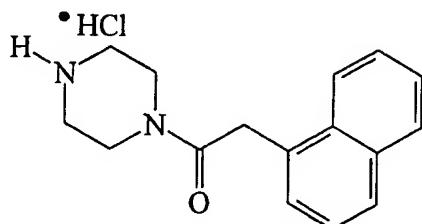
where the amount is effective to enhance the sexual performance of the patient.

6. The use of claim 5 wherein the compound provides a pro-erectile response in the patient.

7. The use of claim 1, 2, 3, 4, 5 or 6 wherein R<sup>1</sup> or L is a direct bond.

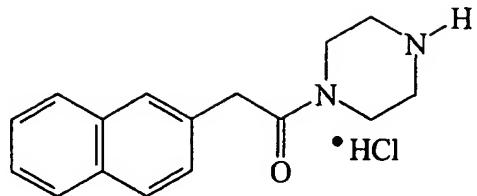
8. The use of claim 1, 2, 3, 4, 5 or 6 wherein R<sup>1</sup> and L are both direct bonds.

9. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound has the formula



including salts, solvates, isolated tautomers, and mixtures thereof.

10. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound has the formula



including salts, solvates, isolated tautomers, and mixtures thereof.

11. The use of claim 1, 2, 3, 4, 5 or 6 wherein L is selected from the group of O, NH and NCH<sub>3</sub>

12. The use of claim 1, 2, 3, 4, 5 or 6 wherein R<sup>1</sup> is a 1,2-disubstituted cyclohexane or a 1,2-disubstituted cyclopentane.

13. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound is formulated for oral administration.

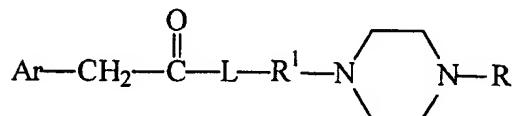
14. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound is formulated for topical administration.

15. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound is formulated for direct injection.

16. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound is formulated for one of intrameatal, intracavernous or intraurethral administration.

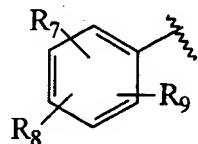
17. The use of claim 1, 2, 3, 4, 5 or 6 wherein the compound is formulated as a tablet with a disintegration time of less than one hour.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of the formula



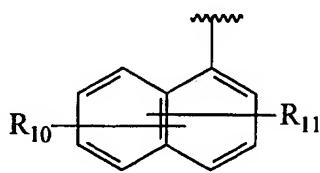
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):

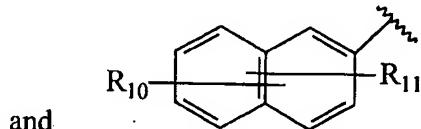


(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

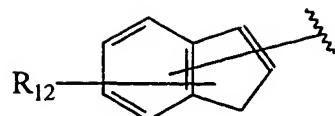


(III)



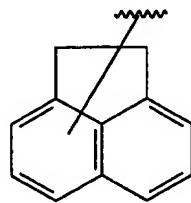
(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

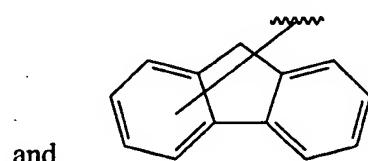


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxycarbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



(VI)



(VII);

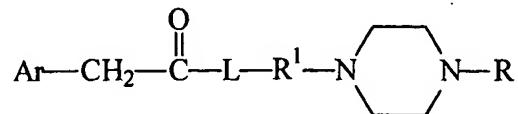
$L$  is selected from the group of a direct bond, O, NH, and  $N(C_1-C_6$  alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$  alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$  cycloalkyl; and

$R$  is H or a  $C_7$ - $C_{13}$  aralkyl;

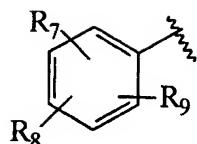
wherein the composition is in the form of a tablet for oral administration, and the tablet has a disintegration time of less than one hour.

19. A method for treating or preventing sexual dysfunction in a patient, comprising administering to the patient in need thereof an amount of a compound of the formula



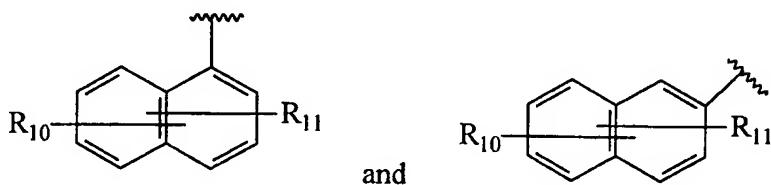
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

$\text{Ar}$  is selected from a  $C_3$ - $C_{13}$  carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):



(II)

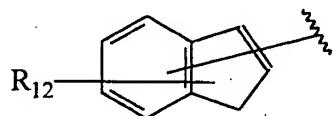
where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;



(III)

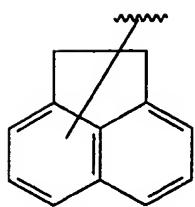
(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;

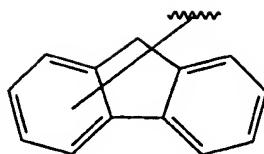


(V)

where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl; and



(VI)



(VII);

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub>alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and

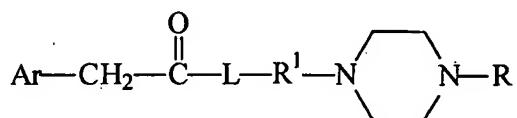
R is H or a C<sub>7</sub>-C<sub>13</sub>aralkyl;

where the amount is effective to treat or prevent the sexual dysfunction of the patient.

20. The method of claim 19 wherein the sexual dysfunction is male erectile dysfunction.

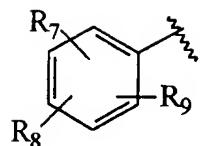
21. The method of claim 19 wherein the sexual dysfunction is impotence.

22. A method for increasing the libido of a male or female patient, comprising administering to the patient in need thereof an amount of a compound of the formula



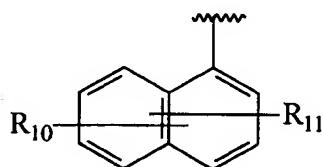
including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub>carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):



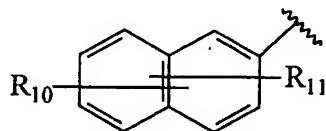
(II)

where  $R_7$ ,  $R_8$  and  $R_9$  are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, aryl and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl;



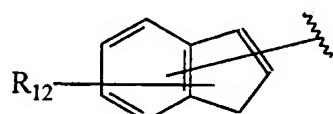
(III)

and



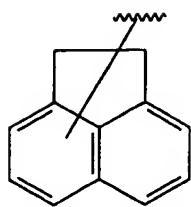
(IV)

where  $R_{10}$  and  $R_{11}$  are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl;

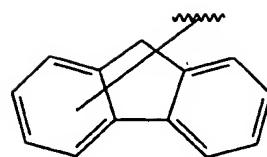


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



(VI)



(VII);

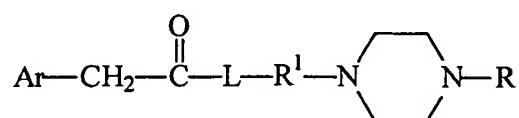
L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and

R is H or a C<sub>7</sub>-C<sub>13</sub> aralkyl;

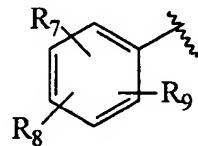
where the amount is effective to increase the libido of the patient.

23. A method for enhancing the sexual performance of a male or female patient, comprising administering to the patient in need thereof an amount of a compound of the formula



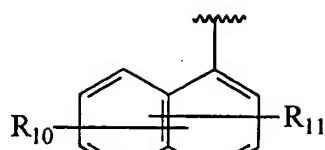
including salts, solvates, isolated enantiomers, isolated diastereomers, and mixtures thereof, wherein, independently at each occurrence:

Ar is selected from a C<sub>3</sub>-C<sub>13</sub> carbocyclic ring, and ring systems selected from formulae (II), (III), (IV), (V), (VI), and (VII):

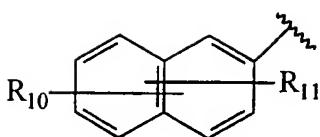


(II)

where R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub> alkanoyloxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>7</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> thioalkyl, aryl and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub> alkyl;

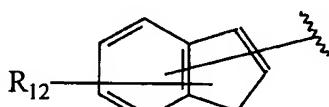


(III)



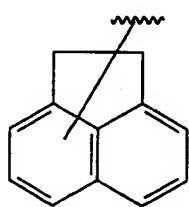
(IV)

where R<sub>10</sub> and R<sub>11</sub> are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl;

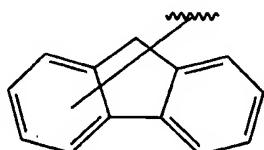


(V)

where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxy carbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15}, R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and



(VI)



(VII):

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$ alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$ cycloalkyl; and

R is H or a C<sub>7</sub>-C<sub>13</sub> aralkyl;

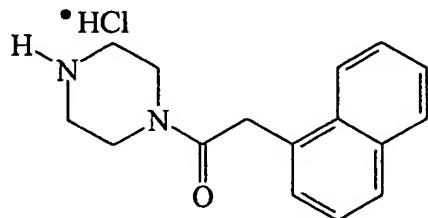
where the amount is effective to enhance the sexual performance of the

24. The method of claim 23 wherein the compound provides a pro-erectile response in the patient.

25. The method of claims 19, 22 or 23 wherein R<sup>1</sup> or L is a direct bond.

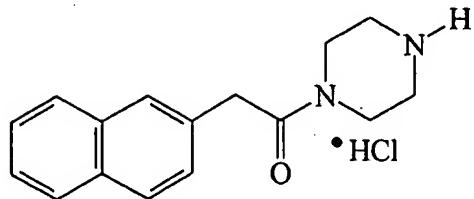
26. The method of claims 19, 22 or 23 wherein R<sup>1</sup> and L are both direct bonds.

27. The method of claims 19, 22 or 23 wherein the compound has the formula



including salts, solvates, isolated tautomers, and mixtures thereof.

28. The method of claims 19, 22 or 23 wherein the compound has the formula



including salts, solvates, isolated tautomers, and mixtures thereof.

29. The method of claims 19, 22 or 23 wherein L is selected from O, NH and NCH<sub>3</sub>.

30. The method of claims 19, 22 or 23 wherein R<sup>1</sup> is a 1,2-disubstituted cyclohexane or a 1,2-disubstituted cyclopentane.

31. The method of claims 19, 22, or 23 wherein the administration is by oral administration.

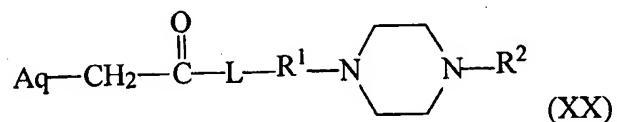
32. The method of claims 19, 22, or 23 wherein the administration is by topical administration.

33. The method of claims 19, 22, or 23 wherein the administration is by direct injection.

34. The method of claims 19, 22, or 23 wherein the administration is by one of intrameatal, intracavernous or intraurethral administration.

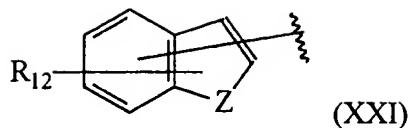
35. The method of claims 19, 22, or 23 wherein the compound is formulated as a tablet with a disintegration time of less than one hour.

36. A compound of formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system of the formula (XXI)



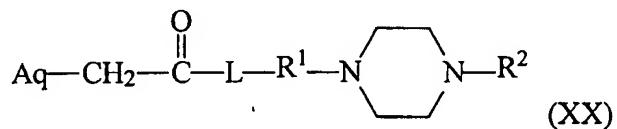
where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxycarbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and  $Z$  is selected from O, N and S, where  $Z$  may be directly bonded to “- $CH_2C(O)-L-$ ” as shown in formula (XX) when  $Z$  is N, or  $Z$  may be directly bonded to  $R_{17}$  when  $Z$  is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl, aryl and benzyl;

$L$  is selected from the group of a direct bond, NH, and  $N(C_1-C_6\text{alkyl})$ ;

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$  alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$  cycloalkyl; and

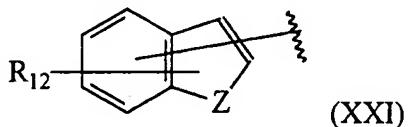
$R^2$  is selected from the group of H, a  $C_1$ - $C_6$  alkyl and a  $C_7$ - $C_{13}$  aralkyl.

37. The use of a compound for the manufacture of a medicament for the treatment or prevention of sexual dysfunction in a patient, the compound having the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

$Aq$  is a heterocyclic ring system of the formula (XXI)



where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_7$  alkanoyloxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_7$  alkoxycarbonyl,  $C_1$ - $C_6$  thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$  alkyl; and  $Z$  is selected from O, N and S, where  $Z$  may be directly bonded to “- $CH_2C(O)-L-$ ” as shown in formula (XX) when  $Z$  is N, or  $Z$  may be directly bonded to  $R_{17}$  when  $Z$  is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl, aryl and benzyl;

$R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl; and  $Z$  is selected from O, N and S, where  $Z$  may be directly bonded to “- $CH_2C(O)-L-$ “ as shown in formula (XX) when  $Z$  is N, or  $Z$  may be directly bonded to  $R_{17}$  when  $Z$  is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_3$ - $C_8$ cycloalkyl, aryl and benzyl;

$L$  is selected from the group of a direct bond, O, NH, and  $N(C_1$ - $C_6$ alkyl);

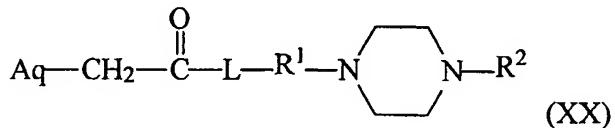
$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$ alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$ cycloalkyl; and

$R^2$  is selected from the group of H, a  $C_1$ - $C_6$ alkyl and a  $C_7$ - $C_{13}$ aralkyl;

where the amount is effective to treat or prevent the sexual dysfunction of the patient.

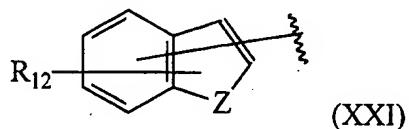
38. The use of claim 37 wherein the sexual dysfunction is male erectile dysfunction or impotence.

39. The use of a compound for the manufacture of a medicament for increasing the libido of a male or female patient, the compound having the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

$Aq$  is a heterocyclic ring system of the formula (XXI)



where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_6$ alkanoyloxy,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ alkoxy,  $C_2$ - $C_6$ alkoxycarbonyl,  $C_1$ - $C_6$ thioalkyl, and  $N(R_{15}, R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl; and  $Z$  is selected from O, N and S, where  $Z$  may be directly bonded to “- $CH_2C(O)-L-$ “ as shown in

formula (XX) when Z is N, or Z may be directly bonded to R<sub>17</sub> when Z is N, and R<sub>17</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, aryl and benzyl;

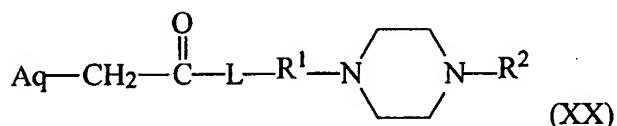
L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub>alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub>cycloalkyl; and

R<sup>2</sup> is selected from the group of H, a C<sub>1</sub>-C<sub>6</sub>alkyl and a C<sub>7</sub>-C<sub>13</sub>aralkyl;

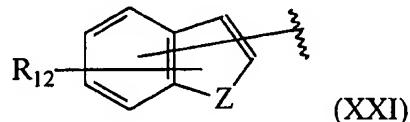
where the amount is effective to increase the libido of the patient.

40. The use of a compound for the manufacture of a medicament for enhancing the sexual performance of a male or female patient, the compound having the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system of the formula (XXI)



where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>7</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, acetyl, methanesulfonyl, and C<sub>1</sub>-C<sub>6</sub>alkyl; and Z is selected from O, N and S, where Z may be directly bonded to "-CH<sub>2</sub>C(O)-L-" as shown in formula (XX) when Z is N, or Z may be directly bonded to R<sub>17</sub> when Z is N, and R<sub>17</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, aryl and benzyl;

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$ alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$ cycloalkyl; and

$R^2$  is selected from the group of H, a  $C_1$ - $C_6$ alkyl and a  $C_7$ - $C_{13}$ aralkyl;

where the amount is effective to enhance the sexual performance of the patient.

41. The use of claim 40 wherein the compound provides a pro-erectile response in the patient.

42.

43. The use of claim 37, 38, 39, 40 or 41 wherein  $R^1$  and L are both direct bonds.

44. The use of claim 37, 38, 39, 40 or 41 wherein the compound is selected from the group consisting of:

1-methyl-4-(2-benzofuranacetyl)piperazine monohydrochloride;

1-methyl-4-(3-indolacetyl)piperazine monohydrochloride;

1-methyl-4-(3-benzo[b]thiophenacetyl)piperazine monohydrochloride;

and other pharmaceutically acceptable salts or solvates thereof.

45. The use of claim 37, 38, 39, 40, 41 or 44 wherein the compound is formulated for oral administration.

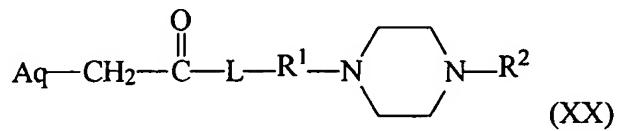
46. The use of claim 37, 38, 39, 40, 41 or 44 wherein the compound is formulated for topical administration.

47. The use of claim 37, 38, 39, 40, 41 or 44 wherein the compound is formulated for direct injection.

48. The use of claim 37, 38, 39, 40, 41 or 44 wherein the compound is formulated for one of intrameatal, intracavernous or intraurethral administration.

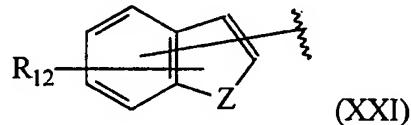
49. The use of claim 37, 38, 39, 40, 41 or 44 wherein the compound is formulated as a tablet with a disintegration time of less than one hour.

50. A method for treating or preventing sexual dysfunction in a patient, comprising administering to the patient in need thereof an amount of a compound of the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system of the formula (XXI)



where  $\text{R}_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $\text{C}_2\text{-C}_6$  alkanoyloxy,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_2\text{-C}_6$  alkoxy carbonyl,  $\text{C}_1\text{-C}_6$  thioalkyl, and  $\text{N}(\text{R}_{15},\text{R}_{16})$  where  $\text{R}_{15}$  and  $\text{R}_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $\text{C}_1\text{-C}_6$  alkyl; and Z is selected from O, N and S, where Z may be directly bonded to “ $-\text{CH}_2\text{C}(\text{O})-\text{L}-$ ” as shown in

formula (XX) when Z is N, or Z may be directly bonded to R<sub>17</sub> when Z is N, and R<sub>17</sub> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, aryl and benzyl;

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and

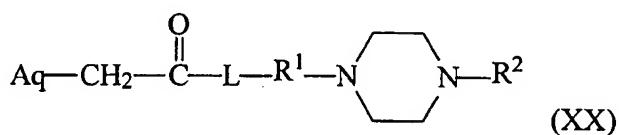
R<sup>2</sup> is selected from the group of H, a C<sub>1</sub>-C<sub>6</sub> alkyl and a C<sub>7</sub>-C<sub>13</sub>aralkyl;

where the amount is effective to treat or prevent the sexual dysfunction of the patient.

51. The method of claim 50 wherein the sexual dysfunction is male erectile dysfunction.

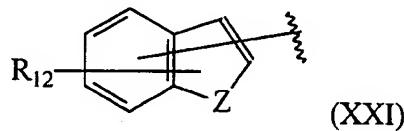
52. The method of claim 50 wherein the sexual dysfunction is impotence.

53. A method for increasing the libido of a male or female patient, comprising administering to the patient in need thereof an amount of a compound of the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system of the formula (XXI)



where R<sub>12</sub> is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C<sub>2</sub>-C<sub>6</sub>alkanoyloxy, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>2</sub>-C<sub>7</sub>alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>thioalkyl, and N(R<sub>15</sub>,R<sub>16</sub>) where R<sub>15</sub> and

$R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl; and Z is selected from O, N and S, where Z may be directly bonded to “- $CH_2C(O)-L-$ “ as shown in formula (XX) when Z is N, or Z may be directly bonded to  $R_{17}$  when Z is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_3$ - $C_8$ cycloalkyl, aryl and benzyl;

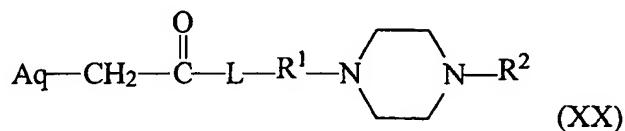
L is selected from the group of a direct bond, O, NH, and  $N(C_1$ - $C_6$  alkyl);

$R^1$  is selected from the group of a direct bond, a  $C_1$ - $C_6$  alkylene group, and a 1,2-disubstituted  $C_5$ - $C_6$  cycloalkyl; and

$R^2$  is selected from the group of H, a  $C_1$ - $C_6$  alkyl and a  $C_7$ - $C_{13}$  aralkyl;

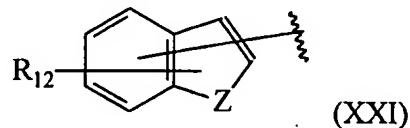
where the amount is effective to increase the libido of the patient.

54. A method for enhancing the sexual performance of a male or female patient, comprising administering to the patient in need thereof an amount of a compound of the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system having the formula (XXI)



where  $R_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $C_2$ - $C_6$  alkanoyloxy,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ alkoxy,  $C_2$ - $C_7$ alkoxycarbonyl,  $C_1$ - $C_6$ thioalkyl, and  $N(R_{15},R_{16})$  where  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $C_1$ - $C_6$ alkyl; and Z is selected from O, N and S, where Z may be directly bonded to “- $CH_2C(O)-L-$ “ as shown in formula (XX) when Z is N, or Z may be directly bonded to  $R_{17}$  when Z is N, and  $R_{17}$  is selected from hydrogen,  $C_1$ - $C_6$ alkyl,  $C_3$ - $C_8$ cycloalkyl, aryl and benzyl;

L is selected from the group of a direct bond, O, NH, and N(C<sub>1</sub>-C<sub>6</sub> alkyl);

R<sup>1</sup> is selected from the group of a direct bond, a C<sub>1</sub>-C<sub>6</sub> alkylene group, and a 1,2-disubstituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl; and

R<sup>2</sup> is selected from the group of H, a C<sub>1</sub>-C<sub>6</sub> alkyl and a C<sub>7</sub>-C<sub>13</sub> aralkyl;

where the amount is effective to enhance the sexual performance of the patient.

55. The method of claim 54 wherein the compound provides a pro-erectile response in the patient.

56. The method of claim 50, 53 or 54 wherein R<sup>1</sup> or L is a direct bond.

57. The method of claim 50, 53 or 54 wherein R<sup>1</sup> and L are both direct bonds.

58. The method of claim 50, 53 or 54 wherein L is selected from O, NH or NCH<sub>3</sub>.

59. The method of claim 50, 53 or 54 wherein R<sup>1</sup> is a 1,2-disubstituted cyclohexane or a 1,2-disubstituted cyclopentane.

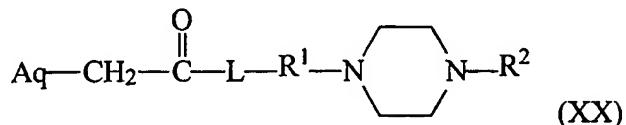
60. The method of claim 50, 53 or 54 wherein the administration is by oral administration.

61. The method of claim 50, 53 or 54 wherein the administration is by topical administration.

62. The method of claim 50, 53 or 54 wherein the administration is by direct injection.

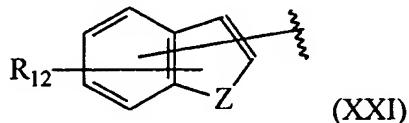
63. The method of claim 50, 53 or 54 wherein the administration is by one of intrameatal, intracavernous and intraurethral.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of the formula (XX)



including salts, solvates, isolated enantiomers, isolated diastereomers, isolated tautomers, and mixtures thereof, wherein, independently at each occurrence:

Aq is a heterocyclic ring system having the formula (XXI)



where  $\text{R}_{12}$  is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,  $\text{C}_2\text{-C}_7$  alkanoyloxy,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_2\text{-C}_7$  alkoxycarbonyl,  $\text{C}_1\text{-C}_6$  thioalkyl, and  $\text{N}(\text{R}_{15},\text{R}_{16})$  where  $\text{R}_{15}$  and  $\text{R}_{16}$  are independently selected from hydrogen, acetyl, methanesulfonyl, and  $\text{C}_1\text{-C}_6$  alkyl; and  $\text{Z}$  is selected from O, N and S, where  $\text{Z}$  may be directly bonded to " $-\text{CH}_2\text{C}(\text{O})-\text{L}-$ " as shown in formula (XX) when  $\text{Z}$  is N, or  $\text{Z}$  may be directly bonded to  $\text{R}_{17}$  when  $\text{Z}$  is N, and  $\text{R}_{17}$  is selected from hydrogen,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_3\text{-C}_8$  cycloalkyl, aryl and benzyl;

$\text{L}$  is selected from the group of a direct bond, O, NH, and  $\text{N}(\text{C}_1\text{-C}_6$  alkyl);

$\text{R}^1$  is selected from the group of a direct bond, a  $\text{C}_1\text{-C}_6$  alkylene group, and a 1,2-disubstituted  $\text{C}_5\text{-C}_6$  cycloalkyl; and

$\text{R}^2$  is selected from the group of H, a  $\text{C}_1\text{-C}_6$  alkyl and a  $\text{C}_7\text{-C}_{13}$  aralkyl;

wherein the composition is in the form of a tablet for oral administration, and the tablet has a disintegration time of less than one hour.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: ACETYLPIPERAZINES FOR MODULATING SEXUAL ACTIVITY

## (57) Abstract

The present invention discloses that substituted acetic acid derivatives containing a piperazine moiety are useful as pro-libido agents for males and females, and may be used for the treatment of sexual dysfunction including erectile dysfunction and impotence and to enhance sexual performance.

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BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

Inten. Application No  
PCT/US 99/15571

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 7 A61K31/495 C07D307/79 C07D333/60 C07D209/18**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 7 A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>"The pro-erectile project"  <b>NORTRAN PHARMACEUTICALS INTERNET SITE,</b>          'Online! XP002132463          Retrieved from the Internet:  &lt;URL:<a href="http://www.nortran.com/projects/PE.html">http://www.nortran.com/projects/PE.html</a>&gt; 'retrieved on 2000-02-09!          figure 1</p> <hr/>	1-35
X	<p>HAYES E S ET AL: "ACTIONS OF  <b>ARYLPIPERAZINES ON CORPUS CAVERNOSUM</b>  <b>SMOOTH MUSCLE IN VITRO"</b>  <b>ASIA PACIFIC J. PHARMACOL.</b>,          vol. 12, no. 3-4, 1997, pages 97-103,          XP000874585          the whole document  (RSD992)</p> <hr/> <p style="text-align: center;">-/-</p>	1-8, 13-26, 31-35

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

7 March 2000

10/04/2000

Name and mailing address of the ISA

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Authorized officer

Orviz Diaz, P

## INTERNATIONAL SEARCH REPORT

International Application No PCT/US 99/15571
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E.S. HAYES ET AL.: "The effects of 5HT agonists on central peripheral and local erectile pathways" INT. J. IMPOT. RES., vol. 9, no. suppl., 1997, page s34 XP000878783 abstract A8	1-8, 13-26, 31-35
X	E.S. HAYES ET AL.: "RSD 992 enhances erection and copulation in rats and erection in primates" INT. J. IMPOT. RES., vol. 8, no. 3, 1996, page 189 XP000879354 abstract P24	1-8, 13-26, 31-35
P, X	WO 99 02159 A (NORTAN PHARMACEUTICALS INC ;ZOLOTOY ALEXANDER B (CA); HAYES ERIC) 21 January 1999 (1999-01-21) the whole document	1-35
X	WO 95 08544 A (UNIV BRITISH COLUMBIA) 30 March 1995 (1995-03-30) examples 13,14 & US 5 637 583 A cited in the application	18
X	DE COSTA, BRIAN R. ET AL: "Synthesis and evaluation of conformationally restricted N-'2-(3,4-dichlorophenyl)ethyl!-N-methyl-2-(1-pyrrolidinyl)ethylamines at sigma receptors. 2. Piperazines, bicyclic amines, bridged bicyclic amines, and miscellaneous compounds" J. MED. CHEM. (1993), 36(16), 2311-20 , 1993, XP002132464 page 2312, scheme I, compounds 21, 25, 26	18
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US BINIECKI, STANISLAW ET AL: "Synthesis of 3-indolylacetyl piperazines and reduction of compounds obtained with lithium aluminum hydride" retrieved from STN Database accession no. 84:59381 CA XP002132467	36
A	RN=58106-90-4 abstract & ROCZ. CHEM. (1975), 49(9), 1585-8 ,1975,	44
	-/-	

## INTERNATIONAL SEARCH REPORT

Intern'l Application No  
PCT/US 99/15571

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAUTER, FRITZ ET AL: "N-Substituted benzo'b!thiophene-3-acetamide and 3-(.beta.- aminoethyl)benzo'b!thiophene" MONATSH. CHEM. (1967), 98(5), 2089-96 , 1967, XP002132465 compound 3	36
A		44
X	CECCARELLI, STEFANO ET AL: "Synthesis of novel 2-substituted-5-oxycoumarans via a direct route to 2,3-dihydro-5-hydroxy-2-benzofuranacetic acids" J. HETERO CYCL. CHEM. (1993), 30(3), 679-90 ,1993, XP002132466 compounds 17 and 21	36

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/15571

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 19-35 and 50-63 because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark:** Although claims 19-35 and 50-63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.  
PCT/US 99/15571

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9902159	A 21-01-1999	AU	8203398 A	08-02-1999
WO 9508544	A 30-03-1995	AU	7650294 A	10-04-1995
		CA	2172513 A	30-03-1995
		EP	0720605 A	10-07-1996
		US	5637583 A	10-06-1997
		US	5885984 A	23-03-1999